105. (New) The vaccine of Claim 103, wherein the additional immunogen is another protein of *Chlamydia.*

106. (New) The vaccine of Claim 103, wherein the additional immunogen is HMW (High Molecular Weight) protein of *Chlamydia trachomatis.*

## REMARKS

All pending claims are cancelled, without prejudice, and replaced by new Claims 79-106. The new claims are directed to certain embodiments of Applicants' invention and are submitted merely to expedite prosecution and obtain allowance of claims covering certain embodiments of the present invention. Applicants fully reserve all rights to prosecute subject matter of the previous claims in a subsequent divisional or continuation application.

The new claims are fully supported by the specification and claims as originally filed and add no new matter.

In particular, new Claim 79 (and Claims 80-90 dependent thereon) recites a vaccine comprising an isolated PMPE polypeptide of *Chlamydia* spp., having a molecular weight between 90 and 115 kDa as determined by SDS polyacrylamide gel electrophoresis wherein said PMPE polypeptide recognizable by an antibody that binds specifically to a polypeptide comprising an amino acid sequence of SEQ ID NO.: 2. Support is found throughout the specification in particular in Sections 3, 5.1, 5.3, 5.4, 5.6 and 5.7 and original Claims 15, 29, 31 and 32.

New Claim 91 recites a vaccine composition comprising an isolated recombinant PMPE polypeptide produced by a method of culturing a host cell containing a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO.: 1 fused to a

nucleotide sequence encoding a histidine ($(H)_6$) domain. Support for this claim is found, e.g., in the specification at page 43, lines, 1-3 and the examples in Section 6, in particular in subsections 6.11, 6.13 and 6.15.

New Claim 92 recites a vaccine comprising an isolated recombinant PMPE polypeptide produced by a method of culturing a host cell containing plasmid M15 pREP (pQE-pmpE-CT) #37 obtained from ATCC accession No. PTA-2462 and recovering said recombinant polypeptide. Support is found in Section 5.1, 5.7 and Section 6, in particular Section 6.11.

New Claim 93 recites a vaccine comprising an isolated PMPE produced by culturing a host cell which encodes a PMPE comprising an amino acid sequence comprising SEQ ID NO.: 2. Support for this claim is found, e.g., in the specification in Section 6, in particular in Sections 6.11, 6.13 and 6.15.

New Claim 94 recites a vaccine comprising an isolated recombinant PMPE polypeptide encoded by a nucleotide acid of SEQ ID No.: 1 fused to a nucleic acid encoding a histidine affinity ($(H)_6$) domain. Support for this claim is found, e.g., in the specification at page 43, lines, 1-3 and the examples in Section 6, in particular in Sections 6.11, 6.13 and 6.15.

New Claim 95 recites a vaccine comprising an isolated recombinant PMPE polypeptide comprising an amino acid sequence comprising SEQ ID NO.: 2. Support for this claim is found, e.g., in the specification in Section 6, in particular in Sections 6.11, 6.13 and 6.15.

New Claims 96-106 recite isolated fragments of PMPE polypeptides as well as vaccine compositions comprising the same. Support is found throughout the specification in particular in Sections 3, 5.2 and 5.7 and original claims 6-10, 20-29 and 31-32.

No new matter is added.

Rejection under Section 112, 1st paragraph

Claims 1-4, 6-7, 15-24, 31-32, 41 and 57-59 remain rejected. The Office Action alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and use the invention. The Office Action alleges that only a single species of PMPE i.e., of amino acid SEQ ID NO.: 2 ( or encoded by a nucleotide sequence of SEQ ID NO.: 1) is disclosed. The claims are stated to encompass mutated sequences, allelic variants, splice variants, homologous proteins to PMPE of SEQ ID NO.: 2 which are allegedly not described.

Applicants respectfully, but emphatically, disagree.

Firstly, the specification discloses two full length PMPE proteins, i.e.: (1) a PMPE protein with SEQ ID NO.: 2 and (2) the PMPE protein encoded in ATCC Deposit PTA-2462 (see page 58 of specification). It is noted that the Office Action admits that the specification fully discloses a PMPE polypeptide comprising SEQ ID No.: 2 (or encoded by a nucleic acid comprising SEQ ID No.: 1). Attention is directed to the Example Section of the specification, in particular to Section 6.11 which describes the construction of plasmid (pQE-pmpE-Ct) #37 (said plasmid deposited in *E. coli* M15pREP and assigned ATCC No. PTA-2462) which contains a nucleic acid insert encoding PMPE. Exhibit A submitted with the Response filed December 3, 2001 presents the amino acid sequence encoded by the PMPE encoding nucleic acid contained in the plasmid of ATCC No. PTA-2462. For convenience a copy of Exhibit A is submitted herewith as Exhibit 1. In addition, Exhibit 1 presents a BLAST comparison between the amino acid sequence of SEQ ID No.: 2 and the amino acid

sequence encoded by the relevant nucleic acid of the plasmid of ATCC No. PTA-2462.[1] In the BLAST analysis, the sequence labeled query is the sequence of the insert of Plasmid M15pREP (pQE-pmpE-Ct) #37. The sequence labeled "subject" is SEQ ID No.: 2. As shown in the BLAST comparison, the two sequences encoding PMPE are at least 90% identical. The PMPE polypeptide encoded by this plasmid differs from SEQ ID No.: 2 at amino acid residues 1-32, 332 (I(V), 369 (N(S), 613 (T(S), 634 (Q(K), 706 (D(E), 722 (S(F), 775 (T(A), and 899-900 (PG(LE).

Attention is directed to the teaching of the specification in subsection 5.10 relating to the Biological Deposits and to the Statement on Behalf of Applicant (Statement submitted with the Response filed December 3, 2001). As indicated in the specification, the plasmid of ATCC No. PTA-2462 has been submitted in accordance with Budapest Treaty requirements and, as indicated in the Statement, all requirements regarding the availability of said deposit are met.

Further, attention is directed to the recent decision of the Court of Appeals for the Federal Circuit in Enzo Biochem v. Gen-Probe, 63 U.S.P.Q 2d 1609, 1614 (Fed. Cir. 2002) which, reversing its earlier decision in Enzo Biochem v. Gen-Probe, 285 F.3d 1013 (Fed. Cir. 2002), emphatically held that "reference in the specification to a deposit in a public depository, which makes its contents accessible to the public. . . constitutes an adequate. . .

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[1] On page 4 of the Office Action, it is stated that Exhibit A shows that BLAST was used to "discover two other species within the scope of the genus". This is plainly wrong. As clearly taught in the specification in Example Section 6.11, the construct ATCC NO.: PTA-2462 was made by the present inventors to recombinantly express the PMPE protein. The BLAST comparison was used simply to illustrate that the protein encoded by the construct indeed expresses a variant of the PMPE protein having SEQ ID NO.: 2 and hence is a member of the claimed genus.

description of the deposited material sufficient to comply with the written description requirement of Section 112, paragraph 1" (emphasis added).

Thus, the present specification fully discloses at least two full length PMPE proteins, i.e., two species of the claimed genus.

Secondly, the specification also discloses PMPE polypeptides comprising PMPE protein fused to an affinity purification tag (see page 40, lines 11-14). This is a third species of the claimed genus.

With regard to fragments claimed in claim 96 (and claims 97-106 dependent thereon), the specification discloses numerous fragments of PMPE in Table 1 (page 18). The specification further discloses, on pages 21-22, chimeric polypeptides comprising PMPE polypeptide fused to heterologous sequences, including chimeric polypeptides comprising PMPE and Hin47, PMPE and HWMP or PMPE and MOMP. The specification further discloses chimeric proteins comprising SEQ ID NO.: 4, 5, 6, 7, 8, 9, 10 and 11 (see page 21, lines 15-18). As shown in Table 1, page 18, SEQ ID NOS.: 4, 5, 6, 7, 8, 9, 10 and 11 are fragments of PMPE of SEQ ID NO.: 2. The specification on page 23, lines 9-15 further discloses fusion proteins comprising PMPE and a protein having adjuvant activity, including fusion proteins comprising PMPE and B subunit of cholera toxin, PMPE and B subunit of *E. coli* heat labile toxin., PMPE and IL-2., PMPE and IL-4, PMPE and IL-10, PMPE and IL-12 and PMPE and interferon. The specification in Sections 5.1, 5.2, 5.3, clearly teaches one skilled in the art to make and use all the claimed PMPE proteins and fragments thereof.

The Office Action alleges on page 4 that it is not routine in the art to screen for multiple substitutions or multiple modification where amino acid modifications can be made with a reasonable expectation of success.

Applicants disagree. The claims are drawn to vaccine compositions containing isolated PMPE proteins which bind to an antibody that specifically binds to SEQ ID NO.: 2. SEQ ID NO.: 2 is an example of a full length PMPE protein. Applicants have demonstrated in a Response filed Dec. 3, 2001 that isolated full length PMPE protein is efficacious in inducing a protective (immune) antibody response for ameliorating disease associated with Chlamydial infection. The specification clearly teaches an assay to determine if a particular peptide or analog is efficacious in inducing an immune response for ameliorating disease associated with Chlamydial infection. See the specification at Section 6.9.2 at page 64, line 23 through page 65, line 24.

Moreover, as demonstrated by the following art, once it is known that a particular protein is efficacious in inducing a protective immune (antibody) response for ameliorating a disease, it is routine to screen protein variants or fragments for the ability to bind to antigen specific antibodies. The following publications also demonstrate that one skilled in the art, at time of the filing of the present application, given its teaching would have had an expectation that fragments or analogs of proteins which react with an antibody that binds to SEQ ID NO.: 2 (such as instantly claimed variants of PMPE) would retain the ability to induce a protective immune response and would be able to determine, without undue experimentation, whether a particular peptide or variant of PMPE retained the ability to elicit a protective immune response.

Deslauriers et al. (Infection and Immunity 64:434, 1996 a copy submitted herewith as Exhibit 2) teaches that immunization of guinea pigs with residues 202-221 of fimbriae protein of *Porphyromonas gingivalis* induces protective immunity to cutaneous lesions caused by *P. gingivalis* local injection (see column 434, second paragraph). Deslauriers et al. also teaches a method of screening synthetic peptides for antigenic and

immunogenetic fragments and that a 20 mer peptide (PgF-P8) corresponding to amino acid residues 103-122 of *P. gingivalis fimbrillin* induces protective immune responses (see page 436-437 and Figures 2-3 and Table 2).

Sexton et al. (J. Of Immunology 152:1861, 1994 a copy of which is submitted herewith as Exhibit 3, already of record as Reference BI) pertains to the use of glutathione S-transferase (GST) as an immunogen for vaccination of animals against parasitic disease. Sexton et al. teaches that the skilled artisan is able to determine if a peptide derived from a protein retains the ability to be antigenic and/or protective. On page 1862, lines 3-19. Sexton teaches that the skilled artisan can select peptides that retain antigenicity and/or immunogenicity on the basis of predictive algorithms which have the ability to induce protective immunity. Sexton et al. also teach on page 1867, right column, other methods known in the art to predict location of epitopes of proteins based upon surface accessibility and temperature effects. Sexton et al. further discloses that a peptide fragment of GST 8 amino acids in length as well as a carboxyl-terminus peptide (corresponding to residues 190-211 of GST) or a amino terminus peptide (corresponding to residues 10-43 GST) induces protective responses (see page 1862 left column lines 5-19).

Briles et al., US Patent No.: 5,964,141 (a copy submitted herewith as Exhibit 4) discloses methods of screening fragments of a protein of protective epitope sand that a region of PspA protein of *Streptococcus pneumoniae* corresponding to amino acid residues 192-260 elicits protective immune responses (see column 6, lines 1-10, column 13, lines 5 through column 16, line 25 and column 16, line 45 through column 17, line 52 and Table VI).

Carlson et al. (Infection and Immunity 65:2080, 1997, a copy submitted herewith as Exhibit 5) teaches that a fragment of SCPA protein of Group a *Streptococcus*

induces protective immune responses (see page 2028 right column through page 2083, 2084-2085 and Figures 7 and 8).

Nilsson et al. (J of Clin. Invest. 101, 2640, 1998 a copy submitted herewith as Exhibit 6) teaches a method of screening fragments of collagen binding adhesin protein from *Staphylococcus aureus* for ability to induce protective immune responses (see page 2642-2643 and Figure 2).

Charles et al. US Patent No.: 5,976,544 (a copy submitted herewith as Exhibit 7) discloses methods of screening fragment sand analogs of P69 protein of *Bordetella pertussis* for protective epitopes. Charles et al. discloses three P69 derived peptides which are 30 or 31 amino acids in length and that these peptides are recognized by monoclonal antibody which reacts to the intact protein. Charles et al. further discloses that these peptides induce protective immune responses (See Figure 7, Tables 1 and 2, column 13 lines, line 11-13, claims 16-20). Peptide 684 is a variant of P69 since it is fragment of P69 which contains a deletion of 6 amino acids (see Figure 7). Charles et al. also discloses that peptide 683 which induces protective immune responses is reactive with a neutralizing monoclonal antibody which is cross reactive with P69 of *B. pertussis* (See column 13, line 15-46).

In summary, the present specification at page 64, line 24 through page 65, line 24 teaches an assay to determine immunogenicity and vaccine efficacy of PMPE proteins or fragments thereof. The publications cited above demonstrate that one with ordinary skill in the art at the time of the invention was made would know how to make and screen fragments or variants of proteins known to induce protective immune responses. Therefore one with skill in the art at the time of the invention would, based upon the teachings of the present invention, be able make fragments or variants of the PMPE of *C. trachomatis* and determine which fragments or variants retain the ability to be recognized by antibody to PMPE protein

having amino acid SEQ ID NO.: 2. One with ordinary skill in the art would also have been able to determine which of these fragments or variants induce protective immune response.

Additionally, one with skill in the art would expect that fragments or analogs of PMPE which are recognizable by antibody that specifically binds to PMPE could be used as diagnostic tools to detect the presence of anti- *C. trachomatis* antibodies or to induce or screen for antibodies which specifically react with *C. trachomatis*. Such antibodies could be used in diagnostic assays.

Thus the state of art at the time of invention was such that it was routine for one with ordinary skill in the to determine if a particular fragment or variant of a protein retains the ability to specifically bind to an antibody specific for a protein comprising SEQ ID No.: 2 or to ameliorate disease associated with a pathogen by inducing a protective immune response against such pathogen. Therefore the specification does provide an adequate written description commensurate in scope with the breadth of the claimed invention. In view of the above argument, Applicants respectfully request that the rejection under 112, first paragraph be withdrawn.

Rejections under Section 102

Stephens

Claims 1-4 and 6 remain rejected and Claims 57-59 and 73-74 are newly rejected under Section 102 as anticipated by Stephens et al., 1998, Science 282: 754-759 (Stephens).

Applicants emphatically disagree.

Stephens teaches the sequence of the entire genome of *Chlamydia trachomatis* and putative open reading frames of the genome. Among the putative open reading frames, Stephens includes opening reading frames of a group or proteins designated PMP proteins.

Stephens merely teaches the open reading frames of a family of PMP proteins and does not demonstrate that these proteins are actually produced by the organism, much less that any proteins were isolated from any organism. Stephens does not teach any isolated protein. Stephens teaches only the open reading frame of PMPE and does not teach any fragment of PMPE nor provide any motivation for making a fragment of PMPE.

Further, Stephens does not teach any vaccine composition combining an isolated full length PMPE protein together with a pharmaceutically acceptable carrier.

Although Applicants do not agree with this rejection nor in any way acquiesce with the rejection or the grounds in which it is based, merely, to advance prosecution, all pending claims (except claims 96-97 which are directed to specific isolated fragments of PMPE) have been amended to be directed to vaccine compositions comprising an isolated protein and a pharmaceutically acceptable carrier. No such compositions are taught by Stephens. Hence this rejection is moot with respect to the present claims. This rejection must be withdrawn. Applicants note, however, that they fully reserve all rights to prosecute the subject matter of previously pending claims and to argue against this rejection should it be raised in a subsequent application.

Longbottom

Claims 1-2, 4, 57-59 and 73-74 are rejected under Section 102(b) as anticipated by Longbottom et al., FEMS Microbiol Lett 164: 111-117 1998 (Longbottom).

The Office Action alleges that claims 1, 2 and 4 are anticipated by the 90k putative outer membrane proteins (POMPs) of *Chlamydia psittaci* taught by Longbottom.

Applicants disagree and submit that this rejection is plainly wrong.

Longbottom describes the electron microscopic localization of a family of putative outer membrane proteins (POMPs) of the ovine abortion subtype of *Chlamydia*

*pstittaci*. As taught by Longbottom, at page 112, left column, line 7-12, the POMPs of their study were identified, isolated and characterized in two previous references, i.e., Reference 8 (Longbottom et al., FEMS Microbiol. Lett 143: 277, 1996, Longbottom A, a copy submitted herewith as Exhibit 8) and Reference 9 (Longbottom et al., Infect. Immun. 66: 1317, 1998, Longbottom B a copy submitted herewith as Exhibit 9). At page 115, left column lines 1-2, the cited Longbottom further discloses that the 90Kd POMPs react with anti-POMP mAbs 181 and 0040 (see Figure 3 of Longbottom) and that the anti-POMP antibody 181 and 0040 are the same antibodies as described in Longbottom B, Exhibit 9). Thus it is evident that the 90kD POMPs proteins that are the subject of Longbottom are the same proteins described in Longbottom B (Exhibit 9). Longbottom B (Exhibit 9) teaches that 90kD proteins comprise 4 POMP proteins designated: POMP90A, POMP90B, POMP91A and POMP91B. The sequences of the POMP proteins of Longbottom are shown in Figure 4, page 1321 of Exhibit 9. POMP90A and POMP90B have the same amino acid sequence.

Attention is directed to Exhibit 10, submitted herewith, which consists of pairwise BLAST analysis of SEQ ID NO.: 2 with the sequence of each of POMP90A, POMP91A and POMP91B. The pairwise analysis reveals that there is approximately 24-25% sequence homolgy between SEQ ID NO.: 2 and any of the proteins taught by Longbottom.

Attention is also directed to Exhibit 11, submitted herewith which consists of pairwise BLAST analysis of the amino acid sequence of the presently described PMPE protein encoded by ATCC PTA-2462 with the sequence of each of the POMP90A, POMP91A and POMP91B of Longbottom. The pairwise analysis reveals that there is approximately 24-25% sequence homology between the PMPE protein encoded by ATCC PTA-2462 and any of the proteins taught by Longbottom. Thus the 90kDa proteins taught by Longbottom do not anticipate the presently claimed invention. Moreover, no vaccine

compositions are taught. For all the above reasons, this rejection is in error and must be withdrawn.

Probst

Claims 1, 6, 15-24, 41 and 75-76 are rejected under Section 102(e) as anticipated by US Patent No.: 6,166,177 to Probst (Probst).

Applicants emphatically disagree. Probst does not teach the presently taught novel PMPE proteins or peptide fragments thereof. The only proteins or peptides disclosed by Probst consist of *Chlamydia* proteins having one amino acid sequence of SEQ ID NOS.: 5-14 of Probst.

Attention is directed to Exhibit 12 submitted herewith which consists of a pairwise BLAST analysis of PMPE protein having SEQ ID NO.: 2 to the sequence of each of SEQ ID NOS.: 5-14 of Probst. Exhibit 13 submitted herewith consists of a pairwise BLAST analysis of the PMPE protein encoded by the insert of PTA-2462 to the sequence each of SEQ ID NOS.: 5-14 of Probst. No significant homology was found between the proteins of SEQ ID NOS.: 5-14 taught by Probst and the presently claimed invention. Thus the proteins taught by Probst do not anticipate the presently claimed invention. For the above reasons, the rejection should be withdrawn.

Rejection under Section 103

Probst in view of Murdin

Claims 1, 31-32 and 77-78 are rejected under Section 103 as obvious in view of Probst in view of Murdin et al., Infect. and Immun. 61: 4406 1993 (Murdin).

The Office Action alleges that Probst teaches pharmaceutical compositions and a vaccine comprising an antigen portion of a Chlamydial antigen. The Office Action

further alleges that Murdin teaches an attenuated poliovirus expressing a neutralization epitope from MOMP of *Chlamydia trachomatis* and a 40kDa outer membrane protein. The Office Action concludes that it would have been obvious to make the claimed invention by combining the composition comprising poliovirus-chlamydia hybrid of Murdin with the proteins taught by Probst.

Applicants disagree and submit this rejection is plainly wrong. Neither Murdin nor Probst teach a PMPE protein or fragment used in the presently claimed compositions. Hence no combination of these references in any way suggests the presently claimed compositions.

Attention is directed to Figure 1, page 4408 of Murdin which teaches the poliovirus-chlamydia hybrids. All poliovirus-chlamydia hybrids of Murdin are hybrids of poliovirus and a fragment of MOMP.

Attention is drawn to Exhibit 14 which consists of a pairwise BLAST analysis of SEQ ID NO.: 2 of the present claims and MOMP of Murdin and a pairwise BLAST analysis of the PMPE protein encoded by PTA-2462 and MOMP of Murdin. MOMP is <u>not</u> PMPE and has no sequence homology to PMPE. Further, the hybrid poliovirus may contain a of fragment of MOMP as shown in Figure 1. Attention is drawn to Exhibit 15 which consists of BLAST analysis SEQ ID NO.: 2 and of the MOMP sequences shown in Figure 1 of Murdin. There is no sequence homology between any of the MOMP fragments incorporated into the polio virus and SEQ ID NO.: 2. Attention is also drawn to Exhibit 16 which consists of BLAST analysis of the PMPE protein encoded by the insert of PTA-2462 to the sequence of each of the sequences shown in Figure 1 of Murdin. There is no sequence homology between any of the MOMP fragments incorporated into the polio virus and the PMPE protein encoded by PTA-2462.

For the reasons discussed above, Probst does not teach PMPE protein of the present invention.

Since neither Murdin nor Probst teaches a PMPE protein, they do not individually or in combination suggest, much less teach, the claimed invention. For the above reasons, the rejection should be withdrawn.

Stephens in view of Schmitt

Claim 74 is rejected under Section 103 as obvious over Stephens in view of Schmitt et al. Molec. Biol. Reports 18: 223, 1993 (Schmitt).

The Office Action alleges that Stephens teaches a protein that is 98% identical to SEQ ID NO.: 2 of the claimed invention. The Office Action further alleges that Schmitt teach affinity purified histidine tagged proteins and concludes that it would have been prima facie obvious to add the histidine tag taught by Schmitt to the protein of Stephens.

Applicants emphatically disagree. Claim 74 is replaced by new Claim 91. As presently claimed, Claim 91 is drawn to a vaccine comprising a recombinant PMPE protein encoded by SEQ ID NO.: 1 or recombinant PMPE polypeptide of SEQ ID NO.: 2 fused to a histidine affinity domain. As explained in detail above, Stephens does not teach any isolated Chlamydia protein. Stephens does not teach a vaccine comprising an isolated recombinant protein nor does Stephens provide any motivation to make a vaccine protein encoded by the PMPE ORF fused to a histidine tag.

Further, attention is directed to Exhibit 17, a copy of PCT publication WO 96/40893 discloses the entire genomic sequence of *H. pylori*. Each ORF is identified by SEQ ID NO.: and the specification identifies 6 of the ORF encoded proteins as potentially useful vaccines. All 6 were expressed and tested in a vaccine model. Only 3/6 were efficacious in inducing an immune response able to ameliorate disease caused by *H. pylori*. Thus, given the teaching of Stephens one skilled in the art would have no reasonable expectation that any of the ORF's disclosed would have any use as a vaccine against

*Chlamydia*. Therefore Stephens in view of Schmitt does not suggest, much less teach, the claimed invention. For the above reasons, the rejection should be withdrawn.

Respectfully submitted,

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Geraldine F. Baldwin (Reg. No.)

**PENNIE & EDMONDS** LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090